PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) **International Patent Classification:** **A61P 25/06, A61K 31/195, A61K 31/505, A61K 31/70, A61P 25/00, A61P 25/02, A61P 25/24**	**A1**	(11) **International Publication Number:** **WO 00/56404** (43) **International Publication Date:** 28 September 2000 (28.09.2000)

(21) **International Application Number:** PCT/GB00/01092

(22) **International Filing Date:** 23 March 2000 (23.03.2000)

(30) **Priority Data:**
9906808.2 24 March 1999 (24.03.1999) GB

(60) **Parent Application or Grant**
KILGOWAN LIMITED [/]; (). HORROBIN, David, Frederick [/]; (). HORROBIN, David, Frederick [/]; ()
. GALLAFENT & CO. ; ().

Published

(54) **Title: FORMULATIONS FOR TREATMENT OF PAIN COMPRISING VITAMIN B12 AND PHENYLANINE**

(54) **Titre: FORMULATIONS POUR LE TRAITEMENT DE LA DOULEUR CONTENANT DE LA VITAMINE B12 ET DE LA PHENYLANINE**

(57) Abstract

Orally administrable formulations containing a vitamin B¿12 component, preferably hydroxocobalamin, and phenylalanine are described. They may be taken at a specified daily dosage to provide 50 to 5000 mg phenylalanine per day and 0.2 to 50 mg of vitamin B¿12 component. They are used to treat pain or chronic fatigue syndrome. Other drugs or essentiel nutrients may be added such as folic acid, glucosamine or an anti-depressant drug as appropriate.

(57) Abrégé

Cette invention a trait à des formulations administrables par voie orale contenant un composant de la vitamine B¿12, de l'hydroxocobalamine de préférence, et de la phénylalanine. Ces formulations, qui peuvent être prises quotidiennement à des dosages indiqués, de manière à apporter de 50 à 5000 mg de phénylalanine et de 0,2 à 50 mg du composant de la vitamine B¿12 par jour, sont utilisées pour soulager la douleur ou traiter un syndrome de fatigue chronique. Il est possible, si nécessaire, d'ajouter d'autres substances médicamenteuses ou des éléments nutritifs essentiels, tels que l'acide folique et la glucosamine, ou un médicament antidépresseur.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61P 25/06, 25/02, 25/24, 25/00, A61K 31/70 // (A61K 31/70, 31:195) (A61K 31/70, 31:505, 31:195) (A61K 31/70, 31:70, 31:195)

A1

(11) International Publication Number: **WO 00/56404**

(43) International Publication Date: 28 September 2000 (28.09.00)

(21) International Application Number: PCT/GB00/01092

(22) International Filing Date: 23 March 2000 (23.03.00)

(30) Priority Data:
9906808.2 24 March 1999 (24.03.99) GB

(71) Applicant *(for all designated States except US)*: KILGOWAN LIMITED [GB/GB]; Simcocks, Ridgeway House, Ridgeway Street, P.O. Box 181, Douglas IM99 1PY, Isle of Man (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: HORROBIN, David, Frederick [GB/GB]; Laxdale Limited, Kings Park House, Laurelhill Business Park, Polmaise Road, Stirling FK7 9JQ (GB).

(74) Agent: GALLAFENT & CO.; 9 Staple Inn, London WC1V 7QH (GB).

(81) Designated States: AU, CA, NZ, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: FORMULATIONS FOR TREATMENT OF PAIN COMPRISING VITAMIN B12 AND PHENYLANINE

(57) Abstract

Orally administrable formulations containing a vitamin B_{12} component, preferably hydroxocobalamin, and phenylalanine are described. They may be taken at a specified daily dosage to provide 50 to 5000 mg phenylalanine per day and 0.2 to 50 mg of vitamin B_{12} component. They are used to treat pain or chronic fatigue syndrome. Other drugs or essentiel nutrients may be added such as folic acid, glucosamine or an anti-depressant drug as appropriate.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Paso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Description

FORMULATIONS FOR TREATMENT OF PAIN COMPRISING VITAMIN B12 AND PHENYLANINE

Pain is a major human problem. It comes in many different forms, such as the pain of an acute injury or surgical procedure, the pain associated with chronic inflammation, for example of the joints, the pain of headaches, including migraine attacks, the pain associated with muscle spasms, and many types of long term, chronic, ill-defined pain. Chronic long-term pain is often associated with nerve damage of one type or another. The nerve damage may result from a medical illness such as diabetes or alcoholism, or from damage to nerves resulting from local physical pressure or injury such as many forms of back pain and lower limb pain, or pain resulting from severance of a nerve with partial regrowth, or pain with no very obvious cause such as fibrositis or fibromyalgia.

Many types of drugs may relieve pain. Currently they fall into six major categories although, as pain mechanisms become better understood, more categories are likely to be discovered. These major categories are the opiates such as morphine, heroin, pethidine, codeine and related compounds; the steroids which work by reducing inflammation; the

non-steroidal anti-inflammatory drugs which inhibit the enzymes cyclo-oxygenase 1, cyclo-oxygenase 2 or both; a group of miscellaneous compounds which sometimes work in the pain associated with nerve damage (neuropathic pain) and whose most important members are the tricyclic antidepressants; anti-migraine agents which often interact with the serotonin system; and a group of compounds which are antagonists of various peptides which are believed to be involved in the production of pain. International publication WO 98/01157 discloses that, in the pain associated with diabetes, the antidepressant lofepramine may be particularly effective, especially when combined with the co-administration of neurotransmitter precursors such as L-phenylalanine and tryptophan and with vitamin B_{12}. Under certain circumstances it was stated that the combination of vitamin B_{12} with one of the neurotransmitter precursors might be beneficial but there is no disclosure of any particular treatment regimes.

We have now surprisingly found that two of the compounds described in the previous application, vitamin B_{12} and phenylalanine, are unexpectedly effective when presented orally in particular ratios and when the vitamin B_{12} is given in a high absolute dose and in a relatively high ratio to phenylalanine as compared to normal therapeutic doses of vitamin B_{12}. We have also found that this oral combination is effective not just in the pain of diabetic neuropathy but in all forms of chronic neuropathy, in pain associated with the spinal column, including low back pain and sciatica, in pain of unknown origin such as trigeminal neuralgia, and in headaches of many different types, including tension headaches and migraines. In addition to pain we have also found it beneficial in chronic fatigue syndromes. Over 80 patients with these various types of pain have been treated with good to

excellent relief in about three quarters. The relief usually begins within 24 to 72 hours of the first dose, sometimes within 6 hours, and then may show further improvement over one to two weeks. The improvement is then maintained indefinitely. Chronic fatigue usually takes about one week to improve initially and then shows further improvement over several weeks or months. In contrast to all other approaches to relieving pain, administration of formulations according to the present invention does not appear to be associated with any significant adverse effects.

Thus in accordance with a first feature of the present invention there is provided an orally administrable formulation containing a vitamin B_{12} component and phenylalanine, in a weight ratio of 1/100 to 1/1000, and wherein the concentrations of each are such as to provide, in a daily specified dosage of the formulation, from 50.0 mg to 5000.0 mg phenylalanine and from 0.2 mg to 50.0 mg vitamin B_{12} component.

The total daily dose of the phenylalanine component may be anything from 50mg to 5000mg, but is preferably from 200mg to 2000mg. The phenylalanine should usually be in the L- or DL-forms. However, recent findings of racemase enzymes in humans which can interconvert D and L amino acids mean that the D-form can also be effective. The total daily dose of the vitamin B_{12} component may be from 0.2mg to 50mg but is preferably from 0.5mg to 5mg. These doses are much higher than oral doses normally used in treating vitamin B_{12} deficiency states. The vitamin B_{12} may be in the form of hydroxocobalamin or cyanocobalamin: however, hydroxocobalamin is the preferred form. This is because hydroxocobalamin is a cyanide antagonist whereas cyanocobalamin is not. Since some forms of nerve damage may be related to cyanide accumulation either because of exposure to toxic cyanide-generating materials or to

nutritional deficiency states when cyanide may accumulate, or to errors of metabolism which may lead to elevated cyanide levels, it is preferable to use hydroxocobalamin as the source of vitamin B_{12}.

Surprisingly, no oral pharmaceutical products containing hydroxocobalamin are presently available. All currently contain cyanocobalamin. The materials may be formulated together in any appropriate dosage form known to those skilled in the art. Appropriate dosage forms include tablets, hard or soft gelatin capsules, powders, micro-encapsulated products, solutions, syrups, emulsions, mousses, gels, or other oral forms known to those skilled in the art. The daily dose may be taken at one time, or divided, for example into two, three or four portions.

The formulations may also contain other drugs or nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the formulation is used to relieve the pain of arthritis. The vitamin B_{12} and phenylalanine act rapidly to relieve the pain whereas the glucosamine helps to provide long term repair of the damaged joints. Folic acid is another ingredient of particular value since it acts synergistically with vitamin B_{12} in several metabolic pathways. When folic acid is included, the ratio of vitamin B_{12} to folic acid should be between 1:4 and 4:1. Since chronic pain is often a feature of depression, an antidepressant drug of any appropriate type may also be added to the formulation in an appropriate dose.

EXAMPLES

1. Tablets containing 200mg L-phenylalanine with

between 2mg and 0.2mg of vitamin B_{12}, either as cyanocobalamin or hydroxocobalamin.

2. Tablets as in 1 but containing 500mg or 1000mg of L-phenylalanine in a ratio to the vitamin B_{12} component of 1/100 to 1/1000.

3-4. Formulations as in 1 and 2 but using hard or soft gelatin capsules

5. A syrup containing 500mg L-phenylalanine and between 5 and 0.5mg of vitamin B_{12} component in 10ml, together with appropriate flavouring.

6-10. Formulations as in 1-4 but in which the L-phenylalanine is replaced by DL-phenyalanine or D-phenylalanine.

11-15. Formulations as in 1-4 in which in addition there is included 100-500mg of glucosamine in an appropriate form as an anti-arthritic agent.

16-20. Formulations as in 1-4 in which other essential nutrients are included, particularly folic acid in a 1:1 ratio with vitamin B_{12}.

21-24. Formulations as in 1-4 in which an antidepressant drug of any type is added in an appropriate dose.

Claims

CLAIMS

1. An orally administrable formulation containing a vitamin B_{12} component and phenylalanine, in a weight ratio of 1/100 to 1/1000, and wherein the concentrations of each are such as to provide, in a daily specified dosage of the formulation, from 50.0 mg to 5000.0 mg phenylalanine and from 0.2 mg to 50.0 mg vitamin B_{12} component

2. A formulation according to Claim 1 wherein the vitamin B_{12} component is hydroxocobalamin.

3. A formulation according to Claim 1 wherein the phenylalanine is L-phenylalanine.

4. A formulation according to Claims 1, 2 or 3 wherein the phenylalanine is DL-phenylalanine, or D-phenylalanine.

5. A formulation according to any one of Claims 1 to 4 wherein the daily specified dosage of the formulation contains 200.0 mg to 2000.0 mg phenylalanine.

6. A formulation according to any one of Claims 1 to 5 wherein the daily specified dosage of the formulation contains 0.5 mg to 5.0 mg of the vitamin B_{12} component.

7. A formulation according to any one of the preceding Claims and additionally containing one or more essential nutrients or drugs.

8. A formulation according to any one of the preceding Claims and additionally containing glucosamine or one or more glucosamine derivatives.

9. A formulation according to any one of the preceding

Claims and additionally containing folic acid or related bioactive derivative.

10. A formulation according to any one of the preceding Claims and additionally containing an anti-depressant drug.

11. A method of treatment of pain or chronic fatigue syndrome which comprises the oral administration of a formulation in accordance of any one of the preceding Claims.

12. A method according to Claim 11 wherein the pain is diabetic pain due to peripheral nerve damage.

13. A method according to Claim 11 wherein the pain is a chest, abdominal, limb, pelvic, back or other pain originating from the spinal column.

14. A method according to Claim 11 wherein the pain is a headache or migraine headache.

INTERNATIONAL SEARCH REPORT

Int. Aonal Application No
PCT/GB 00/01092

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P25/06 A61P25/02 A61P25/24 A61P25/00 A61K31/70
//(A61K31/70,31:195),(A61K31/70,31:505,31:195),(A61K31/70,31:70,
31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 01157 A (WWK TRUST) 15 January 1998 (1998-01-15) cited in the application	1-3,5-7, 10-13
Y	page 4, line 4-26 page 5, line 5-12 page 8, line 7-19 page 9, line 1-7; claims 1-7 page 10, line 10-13 page 10, line 19 -page 11, line 2 page 15, line 24 -page 16, line 3 -/--	1,3,5,7, 9-14

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2000	27/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kanbier, D

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. Appl. No. PCT/GB 00/01092

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WORSLEY A P ET AL: "COMBINED TREATMENT FOR SEVERE DIABETIC NEUROPATHY SYMPTOMS" DIABETIC MEDICINE,GB,JOHN WILEY & SONS, LTD, vol. 15, no. 8, 1998, pages 797-798, XP000886764 ISSN: 0742-3071 the whole document	1,3,5,7, 10-12
X	EP 0 835 660 A (MERCKX GASTON EDMOND FILOMENA) 15 April 1998 (1998-04-15) column 2, line 52 -column 3, line 9 column 6, line 24-42; claims 1,8,12 column 7, line 19-24 column 8, line 3-19	1,3,5,7, 10,11,13
X	US 4 331 145 A (WINTER ARTHUR) 25 May 1982 (1982-05-25)	1,4-7
A	column 5, line 25-39; claims 1,2,4,5	11
X	DE 197 20 818 A (SPORTMEDIZIN TEAM MUENCHEN ARZ) 20 May 1998 (1998-05-20) page 2, line 14-18 page 2, column 50-51; claim 1	1,3,5-7, 9
X	YARYURA: "Phenylethylamine and Glucose in True Depression" JOURNAL OF ORTHOMOLECULAR PSYCHIATRY, vol. 5, no. 3, 1976, page 199-202 XP000925212 page 201, right-hand column page 200, right-hand column	1,2,4,5, 7,10
Y	WO 98 08520 A (SCOTIA HOLDINGS PLC; CARI LODER) 5 March 1998 (1998-03-05) claims 1,6	1,3,5,7, 9-14
A	SIMON K H: "ZUR BEHANDLUNG THERAPIERESISTENTER SCHMERZZUSTAENDE MIT HYDROXOCOBALAMIN" MEDIZINISCHE MONATSSCHRIFT,DE,WISSENSCHAFTLICHE VERLAGSGESELLSCHAFT MBH,, vol. 28, no. 10, 1 October 1974 (1974-10-01), pages 466-468, XP002047638 ISSN: 0025-8474 the whole document	2,6, 11-14
A	GB 2 286 528 A (WOODWARD ROBERT JOHN) 23 August 1995 (1995-08-23) page 1-3, line 17 page 5, line 1-3; claims 1,4,10,11	1,4,7,8, 11-13

-/--

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01092

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 11009 A (LODER CARI) 18 April 1996 (1996-04-18) page 3, line 14-22 page 4, paragraph 1; claims 1-3,6,7,10,14,15,18-20	1-5,7, 10,11,13

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Appl. No. PCT/GB 00/01092

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9801157 A	15-01-1998	AU 3451797 A	02-02-1998
		CA 2259010 A	15-01-1998
		EP 0942751 A	22-09-1999
EP 0835660 A	15-04-1998	NONE	
US 4331145 A	25-05-1982	NONE	
DE 19720818 A	20-05-1998	NONE	
WO 9808520 A	05-03-1998	AU 4025397 A	19-03-1998
		EP 1007053 A	14-06-2000
GB 2286528 A	23-08-1995	NONE	
WO 9611009 A	18-04-1996	AU 710339 B	16-09-1999
		AU 3612695 A	02-05-1996
		CA 2200761 A	18-04-1996
		CZ 9700995 A	12-11-1997
		EP 0784476 A	23-07-1997
		FI 971290 A	02-06-1997
		GB 2308065 A,B	18-06-1997
		HU 77380 A	28-04-1998
		JP 10508583 T	25-08-1998
		NO 971539 A	04-04-1997
		NZ 293642 A	28-10-1998
		PL 319830 A	01-09-1997
		SK 43897 A	05-08-1998
		ZA 9508391 A	06-05-1996